1205

PATENT
Docket No.: **2026-4034US1**

#16
JRP
10/17/94

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Wyndham H. Wilson and Robert E. Wittes
Serial No.	:	08/178,463
Filed	:	January 6, 1994
For	:	**TAXOL TREATMENT OF LYMPHOMAS AND BREAST CANCER**
Group Art Unit	:	1205
Examiner	:	Jerome D. Goldberg

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

TRANSMITTAL OF DECLARATION OF WYNDHAM H. WILSON UNDER 37 C.F.R. § 1.132 TO ACCOMPANY THE AMENDMENT FILED ON SEPTEMBER 12, 1994 IN RESPONSE TO THE APRIL 12, 1994 OFFICE ACTION

Sir:

This Declaration of Wyndham H. Wilson under 37 C.F.R. § 1.132 is transmitted herewith to accompany the Amendment under 37 C.F.R. §§ 1.111 and 1.115, which was filed on September 12, 1994, in response to the April 12, 1994 non-final Office Action for the above-identified application.

Applicants respectfully request entry and consideration of the enclosed Declaration, in conjunction with the responsive amendment and associated remarks, at the time of examination of the above-identified patent application.

No fee is believed to be required for the filing of this Declaration. However, should a fee be required, the Commissioner is hereby authorized to charge Deposit Account No. 13-4500, Order No. 2026-4034US1 for any charges properly

assessable in this application. A DUPLICATE COPY OF THIS PAPER IS ATTACHED.

Respectfully submitted,

MORGAN & FINNEGAN

Date: October 7, 1994

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Express Mail Label EF 440 372 831 US

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10-14-94 126 9/26/94 12X Goldberg

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Applicant(s)	:	Wyndham H. Wilson and Robert E. Wittes	Group Art Unit: 1205
Serial No.	:	08/178,463	Examiner: Jerome D. Goldberg
Filed	:	January 6, 1994	
For	:	Taxol Treatment of Lymphomas and Breast Cancer	

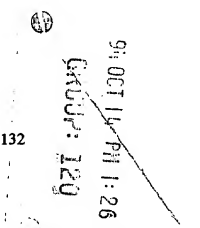
EXPRESS MAIL CERTIFICATE

Express Mail Label No. EF 440 372 831 US

Date of Deposit October 7, 1994

I hereby certify that the following attached paper(s) or fee

1) Transmittal of Declaration of Wyndham H. Wilson under 37 C.F.R. §1.132
2) Declaration under 37 C.F.R. §1.132
3) Return Postcard



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s) : Wyndham H. Wilson and Robert E. Wittes

Serial No. : 08/178,463

Filed : January 6, 1994

For : **TAXOL TREATMENT OF LYMPHOMAS AND BREAST CANCER**

Group Art Unit : 1205

Examiner : Jerome Goldberg

HON. COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

DECLARATION OF WYNDHAM H. WILSON UNDER 37 C.F.R. § 1.132

Sir:

I, Wyndham H. Wilson, M.D., Ph.D., declare that:

1. I am the Special Assistant to the Director, Division of Cancer Treatment, at the National Cancer Institute at the National Institutes of Health. I have held this position for six years.

2. I hold the following degrees: A.B., Stanford University, 1975, in Biology; M.S., Stanford University, 1975, in Biology; Ph.D., Stanford University, 1981, in Neurobiology; and M.D., Stanford University, 1981.

3. I am a co-inventor of the subject matter disclosed and described in the above-identified patent application, and of the subject matter of the claims therein.

4. As one of more than ordinary skill in the art, it is my belief, based on factual information known to me, that there are distinct differences in treatment schedules and

regimens for drug administration, including taxol, and that each dosing schedule or regimen for the administration of a given amount of a drug, such as taxol, over a defined period of time is unique and unobvious in view of other dosing schedules or regimens.

5. It is my further opinion and belief, based on factual information known to me, that the length of time during which taxol is administered to a patient correlates directly with tolerance to the drug, with the efficacy of the drug in affecting target cells, tissues, or organs, and with the ultimate success or failure of the drug treatment. One taxol dosing regimen is not obvious in view of another because each regimen can confer a different treatment outcome, depending on a number of other variables, such as the nature of the individuals being treated and/or assessed, e.g., age; sex; incidences of hypersensitivity reactions; cytotoxicity of taxol; prior therapies; prior or simultaneous combinations of chemotherapies; responses to prior or ongoing therapies; tumor histology; sites of disease; number of disease sites; development of adverse effects, e.g., fever, granulocytopenia, mucositis, death; drug clearance; and numbers of cycles of taxol treatment.

6. It is also my belief, based on factual information known to me, that the individuality of each patient's response to a particular drug dosing schedule or regimen, as well as the virtual "trial and error" process involved with dosing regimens, confer an unpredictability of success or outcome for each schedule studied, until such time as that dosing schedule has been completed and assessed.

7. I have conducted and supervised studies which show that differences exist between the instantly claimed invention and taxol dosing regimens reported in the art, and that one skilled in the art would not be motivated to employ the claimed taxol infusion schedule based on the prior art reports, since the prior art teaches and promotes short infusion times and higher taxol doses, as discussed further herein below.

8. Under my supervision, a Phase I study of taxol infused over 96 hours in accordance with the claimed invention was performed to determine toxicity, maximum tolerated dose (MTD), and pharmacokinetics in patients with incurable lymphomas and metastatic breast cancer. A Phase II study was then performed at the MTD of taxol in patients with metastatic breast cancer that had been shown to be refractive to doxorubicin and/or mitoxantrone treatments.

9. In our Phase I study, taxol dose levels ranged from 120 to 160 mg/m^2 for 96 hours, administered on a 21-day cycle by continuous intravenous infusion. In this study, 140 mg/m^2 was determined to be the MTD.

10. The 96 hour taxol infusion schedule was an inventive discovery, not previously tried in the prior art, and was based on our experimental evidence that prolonged drug exposure of cancer cells to low concentrations of taxol is more cytotoxic than shorter, higher-dose exposure.

11. As mentioned in ¶ 9 *supra*, taxol doses ranged from 120 mg/m^2 to 160 mg/m^2 with a MTD of 140 mg/m^2 in the Phase 1 portion of our study. This MTD was significantly lower than that previously described in Phase 1 trials of 3- and 24-hour infusion schedules in which MTDs ranged from 210 mg/m^2 to 250 mg/m^2 (see P.H. Wiernik et al., 1987, J. Clin. Oncol., 5: 1232-1239, attached as Exhibit 1; and J.H. Schiller et al., 1993 Proc. Am. Soc. Clin. Oncol., 12: 166 (abstr), attached as Exhibit 2).

12. In the Phase II portion of our study, 16/33 (48%) breast cancer patients responded to the claimed taxol dosing regimen (i.e., 140 mg/m^2/96 hours). These patients had breast cancers which were refractory to doxorubicin and/or mitoxantrone.

13. A comparison of our results employing the 96 hour taxol infusion schedule for breast cancer patients with results from a similar type of Phase II study of taxol in either heavily-pretreated breast cancer patients or in patients with doxorubicin-refractory breast cancer is shown in Table 1 below:

Table 1

Source	No. Patients	Treatment Regimen	% Response Rate
Present Invention	33	140 mg/m²/96 h	48
A.D. Seidman et al., 1993, Sem. in Oncol., 20:40-45 (attached as Exhibit 3)	51	250 mg/m²/24 h	22

The results of our studies showed that 96 hour taxol infusion is effective and well-tolerated in breast cancer patients whose disease had progressed during or after standard chemotherapy. These results differ from a similar type of study in the art and indicate that the activity of taxol is highly likely to be schedule-dependent.

14. In studies of drug dosing, dose-dependent clearance of the drug is monitored and is important to the success of a dosing regimen in humans. To determine taxol clearance, we measured the pharmacokinetics of taxol administered at 140 mg/m²/96 h in our studies. Under our taxol dosing conditions, a significantly higher clearance of taxol was observed compared with dosing regimens which employed higher amounts of taxol for shorter infusion times. (see Table 2 below).

Table 2

Source	Liver Disease	No. Patients	Taxol Dose	Taxol Clearance (mL/min/m²) (mean +/- SE)
Present Invention	--	13	140 mg/m²/96 h	470.9 ± 17.4
Present Invention	+	3	140 mg/m²/96 h	324.7 ± 41.2

Present Invention	++	9	140 mg/m²/96 h	335.6 ± 38.2
M.T. Huizing et al., 1993, J. Clin. Oncol., 11:2127-2135, (attached as Exhibit 4)		5	175 mg/m²/3 h	199
		4	175 mg/m²/24 h	393

15. Another important finding in our studies was the association between metastatic liver disease and taxol clearance. This finding further emphasizes the nonobviousness of a dosing regimen due to ancillary factors and/or variables that must be considered in the testing of such regimens (see ¶ 5 *supra*). As shown by the results of our studies reported in Table 2, in 13 patients who did not have detectable liver metastases (--), taxol administered at 140 mg/m²/96 h was cleared at a mean rate of 471 mL/min/m² compared with mean rates of 325 and 336 mL/min/m² in patients with modest (+) or extensive (++) metastatic liver disease, respectively. This suggests that hepatic clearance of taxol may be affected by even modest liver involvement. In contrast, Huizing et al. found lower taxol clearance from patients using taxol dosing at 175 mg/m² for 3 hours and at 175 mg/m² for 24 hours.

16. Based on factual evidence known to me and to those having skill in the art, the art teaches away from a longer taxol infusion time, and instead reinforces a 24 hour dosing schedule using higher doses of taxol e.g., 315-390 mg/m² (Rowinsky et al.) and 250 mg/m² (Holmes et al.); (see E.K. Rowinsky et al., 1989, Cancer Res. 49, 4640-4647, of record, and F.A. Holmes, 1991, J. Natl Cancer Inst., 83: 1797-1805, of record).

17. Indeed, at the September 1993 meeting of the FDA's Oncology Drugs Advisory Committee, the Committee agreed that taxol should be infused over 3 hours rather than the currently recommended 24 hours. The 3 hour taxol infusion time was recommended because

the Committee decided that the shorter infusion time would be less toxic and more convenient to use.

18. Taxol for medical and clinical use is currently labeled with a recommended dosage schedule of 135 mg/m^2 over 24 hours. Bristol-Myers Squibb Co., Princeton, N.J., the current leading distributor of taxol (i.e., Paclitaxel), has adopted the 3-hour taxol dosing schedule and has submitted a Supplemental NDA proposing that the taxol dosing schedule be changed to 175 mg/m^2 over 3 hours.

19. Thus, the presently claimed invention is indicative of a solution to the grave problem of breast cancer that is contrary to conventional ideas both at the time of the invention and at the present time. Accordingly, it is my opinion and belief that this trend toward shorter rather than longer taxol dosing regimens is a strong indicium of the nonobviousness of the presently claimed invention in view of the art.

20. I declare further that all statements made in this Declaration are of my own knowledge and are true and all statements made on information and belief are believed to be true and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 10/4/94

Wyndham H. Wilson

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